

**REMARKS/ARGUMENTS****I. Rejections of Claims 13 and 15-23 under 35 U.S.C. § 112, second paragraph**

Claims 13, 15-23 are rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, The Office Action asserts that the word "KPV" or a "KPV composition" is vague and indefinite.

Applicants have amended claims 13 and 15-23 and replaced the word "KPV" with "a KPV". It is clear from the specification that "a KPV" is the C-terminal tripeptide of  $\alpha$ -MSH consisting of the amino acid sequence  $\text{NH}_2\text{-Lys-Pro-Val-CONH}_2$ . See, P. 7, ll. 23-24. In addition, in the amended claims, a KPV composition comprises a KPV and a carrier. Therefore, the amended claims meet the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request that the rejections of claims 13 and 15-23 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

**II. Rejections of Claims 13 and 15 under 35 U.S.C. § 112, second paragraph**

Claims 13 and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. Specifically, the Office Action asserts that the claims are incomplete for omitting essential positive method steps and such omission amounts to a gap between the steps.

Applicants have amended claims 13 and 15 to include a positive method step. Accordingly, Applicants respectfully request that the rejections of claims 13 and 15 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

**III. Rejection of Claims 13 and 15-23 under 35 U.S.C. § 103 (a).**

Claims 13 and 15-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lipton (U.S. Pat. No. 5,157,023, 1992). To the extent that the rejections can be applied to the amended claims, Applicants respectfully traverse.

The Office Action states that Lipton teaches a tripeptide bearing the amino acid sequence of KPV as an antipyretic and/or anti-inflammatory agent and that Lipton

provides a pharmaceutical composition useful in the treatment of pyrexia and inflammation. While the Office Action admits that Lipton does not teach the administration of a KPV to HIV-infected patients, the Office Action nevertheless concludes that "it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to treat HIV-infect patients suffering from secondary infections with the compounds of Lipton" since "this would reduce the fever and swelling associated with such opportunistic infections."

The very point of the reasoning of the Office Action is based on the assumptions that 1) fever and inflammation are always and necessarily associated with infections and 2) it is within the knowledge of ordinary skilled artisan that an anti pyretic/anti-inflammatory agent can always used to treat infections. The assumptions are unsustainable.

There is an important distinction among fever, infection and inflammation. According to Stedman's Medical Dictionary (25<sup>th</sup> Ed.), infection is defined as "multiplication of parasitic organisms within the body". Inflammation is defined as "a fundamental pathologic process consisting of a dynamic complex of cytological and histological reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biological agent, including; 1) local reactions and resulting morphological changes, 2) the destruction or removal of the injurious materials, and 3) the responses that lead to repair and healing." According to The Merck Manual (16<sup>th</sup> Ed.), fever is defined as an elevation of body temperature above the normal daily variation and the cause "may be infectious or noninfectious." By definition, there is no indication that fever and/or inflammation are necessarily associated with infectons. Fever and inflammation may or may not be associated with infections. For example, it is well known in the art that there are a number of fever and/or inflammation not associated with infections (e.g., rheumatoid arthritis). By the same token, the secondary infections in a HIV-infected individual may or may not be associated with fever and/or inflammation.

It is not true that an anti pyretic/anti-inflammation agent can always be used to treat infections. As a typical example, aspirin has long been regarded as an antipyretic/anti-inflammatory agent but not an anti-infectious agent. Prior to the claimed

invention was made, there was not teaching or suggestion, explicitly or implicitly, that a KPV has an anti-infection property.

Since the Office Action's reasoning is not sustainable, Applicants find no reason why it would be *prima facie* obvious to an ordinarily skilled artisan at the time the invention was made to treat HIV-infected patients suffering from secondary infections with the compounds of Lipton.

Perhaps, however, the Office Action merely means to assert that "if an HIV-infected patient is suffering from a fever due to a bacterial infection, there is sufficient motivation and a reasonable expectation of success in the prior art that administration of a KPV-containing compound will reduce the fever thereby ameliorating one of the symptoms associated with the secondary infection." (See, Office Action, P. 5)

Even in the case that fever or inflammation in a HIV-infected patient is caused by secondary infections, the prior art references not only provide no motivation but also teach away from administering a KPV or a KPV composition to the HIV-infected individual suffering from fever/inflammation due to infections. The specification (P. 27. 1 18 to P. 28, l. 2) states:

Reduced killing of pathogens is a dire consequence of therapy with corticosteroids and nonsteroidal anti-inflammatory drugs during infection. Steven, D.L., Could Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Enhance Progression of Bacterial Infections to Toxic Shock Syndrome?, Clin. Infect. Dis 21, 977-80 (1995); Capsoni, F.; Merino, PL; Zocchi, M.R.; Plebani, A.M.; Verzio, M., Effect of Corticosteroids on Neutrophil Function: Inhibition of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), J. Immunopharmacol. 5, 217-30 (1983). This effect could be particularly dangerous in the immunocompromised host.

It is well known in the art that anti-pyretic/anti-inflammation agents can be categorized into two classes of compounds: corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are commonly known to attenuate granulocyte functions such as chemotaxis, phagocytosis and bacterial killings and contribute to aggressive infection by inhibiting neutrophil functions. See the Abstract of Steven, D.L.

Corticosteroids on the other hand, have shown to inhibit neutrophil-mediated antibody-dependent cellular cytotoxicity and thus cause a killing defect. See the Abstract of Capsoni et al. Furthermore, corticosteroids have been reported to stimulate the growth of HIV virus and the expression of HTLV-III. Markham et al., Hydrocortisone and some other hormones enhance the expression of HTLV-III, Int'l J. Cancer 37: 67-72 (1986) (See also the Response and Amendment filed on April 18, 2002). Put together, it is well known in the art that anti pyretic/anti-inflammation compounds cause the reduction of pathogen killings or even the aggravation of infections.

The Office Action concedes that a KPV or a KPV composition is an efficient antipyretic or anti-inflammatory compound. The Office Action's assertion that "the shorter alpha MSH molecule, which is derived from ACTH, does not stimulate steroid release and there appears to be no irreversible deleterious effects when given to rabbit or to man" does not mean that the shorter alpha MSH molecule is free from any adverse effect. Lipton makes no mention about the effect of the shorter alpha MSH molecule on pathogen killings. Quite to the contrary, alpha-MSH is known to inhibit neutrophil chemotaxis. See, Spec. p. 28, ll. 6-9. See also, Catania et al., The Neuropeptide  $\alpha$ -MSH has Specific Receptors on Neutrophils and Reduces Chemotaxis in Vitro, Peptides 17: 675-679 (1996).

Given that a KPV or a KPV composition is an efficient antipyretic or anti-inflammatory compound and that antipyretic/anti-inflammatory compounds are known to reduce pathogen killings or aggravate infections, given further that alpha-MSH is known to inhibit neutrophil chemotaxis, one of ordinary skill in the art could have expected that a KPV or a KPV composition would reduce pathogen killings (See, Spec. P. 28, ll. 10-11). It follows that, had Applicant not made the unexpected discovery that alpha-MSH peptides do not reduce killing but rather enhance it (See, Spec. P. 28, ll. 11-13), one of ordinary skill in the arts could have been discouraged to use a KPV or a KPV composition for the treatment of fever or inflammation in a HIV-infected individual caused by secondary infections due to the fear for an undesired reduction of pathogen killings or an unwanted aggravation of infections.


In sum, the Office Action's reasoning in making a *prima facie* obviousness rejection is unsustainable. Prior to the claimed invention was made, there was no

teaching or suggestion, explicitly or implicitly, that a KPV or a KPV composition has anti-infection properties. The prior art references not only provide no motivation but also teach away from administering a KPV or a KPV composition in treating fever/inflammation in a HIV-infected individual caused by secondary infections. Therefore, the claimed invention is not obvious over Lipton. Applicants respectfully request that the rejections of claims 13 and 15-23 for being obvious over Lipton be reconsidered and withdrawn.

In view of the foregoing, the claims 13, 15-23, and 24-33 are in condition for allowance. Therefore, a Notice of Allowance is respectfully requested.

Respectfully submitted,  
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**APPENDIX**

**VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE  
SPECIFICATION**

Reduced killing of pathogens is a dire consequence of therapy with corticosteroids and nonsteroidal anti-inflammatory drugs during infection. Steven, D.L., Could Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Enhance Progression of Bacterial Infections to Toxic Shock Syndrome?, Clin. Infect. Dis 21, 977-80 (1995[7]); Capsoni, F.; Merino, P.L.; Zocchi, M.R.; Plebani, A.M.; Verio, M., Effect of Corticosteroids on Neutrophil Function: Inhibition of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), J. Immunopharmacol. 5, 217-30 (1983). This effect could be particularly dangerous in the immunocompromised host.

**VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS**

13. (Twice Amended) A method for treating secondary infections in [person with HIV] a HIV-infected individual comprising: [the use of] administering to the individual [KPV or a biologically functional equivalent in ]a pharmaceutically appropriate amount of a KPV, wherein the KPV is anti-microbial.

15. (Amended) The method of claim 13, wherein the KPV [or the biologically functional equivalent] is contained in [one of the carriers from the following] a carrier selected from the group consisting of a solution for injection, a liquid, a pill, a capsule, a cream, an ointment, a gel, a suppository, an aerosol spray, and an inhaler.

16. (Amended) A method for treating secondary infections in a HIV-infected individual comprising: administering a KPV composition in a pharmaceutically appropriate amount to the HIV-infected individual, wherein the KPV composition comprises a KPV and a carrier and the KPV is anti-microbial.

17. (Amended) The method of claim 16, wherein [administration is] the KPV composition is administered orally, parenterally, locally or topically.

18. (Amended) The method of claim 16, wherein the carrier is water, saline, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, petroleum jelly, a solution, suspension, ointment, cream, powder, gel, or aerosol.

20. (Amended) The method of claim 19, wherein the additive is a flavoring[s], a preservative[s], a stabilizer[s], a emulsifier[s], a buffer[s] or a combination thereof.

21. (Amended) The method of claim 16, wherein the pharmaceutically appropriate amount for an oral administration is about 1-10 milligrams/kg.

22. (Amended) The method of claim 16, wherein the pharmaceutically appropriate amount for an intravenous administration is about 1-10 micrograms/kg.

23. (Amended) The method of claim 16, wherein the KPV in the KPV composition comprises 10-40% by weight of the KPV composition for a topical administration.